Approach to patients with aspirin hypersensitivity and acute cardiovascular emergencies

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ABSTRACT

The occurrence of an emergent need for aspirin therapy in an aspirin or nonsteroidal anti-inflammatory drug (NSAID)–"allergic" individual presents one of the more challenging situations the allergist may face. A common request is for the allergist to evaluate an acutely ill patient in a monitored hospitalized setting with a vague and remote history of a "reaction to aspirin." Because of significant diagnostic limitations, introducing aspirin can be very difficult. The concern about the potential for causing anaphylaxis in an acutely ill patient can lead to fear about performing any challenge or desensitization in these patients. The objective of this article was to review the literature regarding aspirin challenges and desensitization in the emergency setting and present a rational approach to administering aspirin to patients that require this drug.

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To complicate an already difficult clinical situation, aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) can lead to a variety of specific and quite different types of hypersensitivity reactions. Before proceeding to diagnostic testing or desensitization, an attempt should be made to characterize the type of reaction. These five types have been previously described[1] and are outlined here:

1. Aspirin-exacerbated respiratory disease (AERD) is a unique disease in which reactions to NSAIDs or aspirin occur in conjunction with sinus disease, nasal polyps, and asthma. Although asthma is not always present, nasal polyps and sinus disease exist in nearly all patients. These patients will typically experience worsening nasal and ocular symptoms as well as asthma symptoms within 1–2 hours of ingestion of a medication that blocks the cyclooxygenase 1 (COX-1) enzyme. Important historical clues to identify these patients are the existence of sinus disease, loss of smell, the presence of reactions to more than one COX-1 inhibitor, and a typical reaction involving the airway.[2]
2. NSAIDs can cause worsening urticaria and angioedema in patients who have active chronic urticaria. These patients likely have a history of tolerating NSAIDs or aspirin but in the midst of their chronic urticaria have worsening of urticaria from the mast cell destabilizing properties of NSAIDs. These patients will have a history of persistent urticaria made worse by NSAIDs and likely have a history of tolerance of NSAIDs when their underlying urticaria was in remission. This COX-1–mediated effect will occur with any NSAID or aspirin.[3]
3. NSAIDs and aspirin can also cause urticaria as a class effect mediated through COX-1. These patients do not have preexisting urticaria and also no evidence of nasal polyps or asthma. As expected by the mechanism, they may have experienced urticaria or angioedema from several members of the NSAID family.
4. NSAIDSs can cause isolated, probable IgE-mediated urticaria and angioedema. These patients will have urticaria and/or angioedema related to one specific NSAID. These reactions are poorly understood, but the specificity of the reaction to one NSAID suggests that a specific IgE mechanism is involved, possibly because of drug haptenization. A history of tolerance of other NSAIDs should highlight this type of reaction as most likely.
5. NSAIDs also can cause anaphylaxis. Similar to the previous category, these reactions are probably IgE mediated but differ from the previous reaction in the severity and scope of the reaction. These reactions are characterized by other components of anaphylaxis such as airway or circulatory compromise. These reactions are limited to a specific NSAID, but because of structural similarity among a family of NSAIDs, cross-reactions may exist. Patients with an IgE-mediated reaction to any other NSAID should not have difficulty taking aspirin. By extension, aspirin has generally been felt to cause similar reactions and has been reported in the literature as a historical cause of anaphylaxis by patients seen in emergency rooms.[4] There is one report of positive

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skin tests to lysyl aspirin in patients with aspirin-induced urticaria.[5] This suggests that aspirin-induced anaphylaxis is a possibility. However, despite an extensive literature search and careful review, peer consultation throughout multiple medical systems, and an exhaustive review of the cases of aspirin reactions in the Scripps Medical System we are unable to find even one convincing case of an anaphylactic reaction to aspirin.

AN EVIDENCED-BASED REVIEW

The greatest limitation when reviewing reported studies in the literature on desensitization in the acute setting is the lack of controls. Most published studies reflect the clinical necessity to perform desensitization in an emergent setting without controls so diagnostic studies such as double-blinded challenges were not performed. Thus, before performing "desensitization" it is almost always unknown whether the patient even has hypersensitivity to aspirin.

A recent study by Fajt and Petrov reviewed nine outpatients requiring aspirin for cardiac diseases.[6] The majority of the patients gave a history of cutaneous reactions associated with the ingestion of aspirin. The authors concluded that these were IgE-mediated reactions to aspirin. As described in their desensitization results, several patients developed mild symptoms at extremely low doses of oral aspirin. This case series highlights the difficulty in interpreting results of desensitization protocols. How many of these patients even had true sensitivity to aspirin if a blinded challenge had been performed? How many of the "reactions" that occurred during desensitization were truly representative of a reaction to the aspirin versus a psychosomatic reaction? In a small sample size, these questions markedly reduce the generalizability of the findings to patients with an "aspirin reaction." Indeed, over the last several years at Scripps Clinic, the authors noted that in the majority of non-AERD patients with a history of a "reaction to aspirin or another NSAID," a directly observed challenge in the Allergy Clinic was negative. Therefore, the original reaction was either misattributed to the drug or the sensitivity disappeared over time.

A variety of other experiences with desensitization for an acute need for aspirin have been published, all with similar rates of "success," and all limited in their interpretation by the aforementioned issues.[7–11] Wong *et al.* evaluated 11 patients requiring aspirin in the acute setting.[7] These patients mostly had cutaneous symptoms although one patient may have had AERD based on the provided history. Rossini *et al.* evaluated 26 patients with acute coronary disease and a history of aspirin allergy.[8] Twenty-three of these patients underwent successful desensitization, but very little of their history of a prior reaction is reported in the article, and no patients had previously undergone a blinded aspirin challenge. Two of the three patients in which desensitization was unsuccessful had chronic urticaria worsened by the ingestion of an NSAID. In total, the literature reports 87 patients who underwent aspirin desensitization in an acute setting.[6–14] Desensitization was judged to be "successful" in 79 patients. However, our interpretation is that most of these patients actually underwent negative challenges and therefore may not have been aspirin sensitive. Four of the eight failures were in patients with preexisting chronic urticaria. There were no significant complications or morbidity associated with any of the desensitization failures.

SCRIPPS CLINIC EXPERIENCE

Given the lack of compelling data that true IgE-mediated reactions to aspirin occur, it is likely that prolonged desensitization protocols starting at extremely low doses are unnecessary. This is in line with our clinical experience at Scripps Clinic over the past 15 years. In an initial evaluation of 30 patients with "aspirin allergy" 24 had a history of urticaria and 6 had a history of anaphylaxis. In the urticaria group, 15 were caused by NSAIDS, and 6 were caused by aspirin. All 6 cases of anaphylaxis were secondary to NSAIDS with none caused by aspirin. All patients underwent an aspirin challenge starting at 30 or 60 mg based on the preference of the treating physician. Doses were doubled every 30–90 minutes until a full 325 mg of aspirin was administered. Twenty-eight patients had a negative challenge, and in two patients, mild urticaria occurred. There were no cases of anaphylaxis. All were successfully treated with aspirin.

In a more recent case series, 11 patients referred to our division for "aspirin allergy" and the need for aspirin treatment were evaluated. All underwent aspirin challenge with a starting aspirin dose of either 30 or 40 mg, and the dose was doubled in 90 minutes. One patient had itching, rhinorrhea, and tearing after the second dose was given. This was easily treated with antihistamines and the final dose of 325 mg was given to ensure that desensitization was complete. One patient developed two small hives after the last dose. No patients reacted to the first dose, and in nine patients, there were no objective signs of a reaction. In all patients, a 325-mg dose concluded the challenge, but patients may have been subsequently placed on lower doses of aspirin at the discretion of their other health care providers.

We present a practical approach to the urgent need for aspirin administration in the patient with a history of an adverse reaction to aspirin or another NSAID. These recommendations are guided both by an exhaustive review of the literature and clinical experience framed by an understanding of the mechanisms of the various aspirin/NSAID reactions.

THE GOAL OF ASPIRIN CHALLENGE/DESENSITIZATION

In almost all settings, the urgent need for aspirin is necessitated by its well-known antiplatelet effect. Because a significant antiplatelet effect is seen at 81 mg of aspirin, the initial goal of reaching this dose is reasonable for most patients. As seen in the Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs - Organization to Assess Strategies in Ischemic Syndromes (CURRENT - OASIS) 7 trial, there was no significant difference in end points between the low dose (75–100 mg of aspirin dose) and high dose (300–325 mg daily of aspirin) on cardiovascular death, myocardial infarction, and stroke at 30 days.[15] Thus, the goal of the allergist should be to get to a dose of 81 mg of aspirin as quickly and safely as possible. In combination with new potent platelet inhibitors such as prasugrel and clopidogrel there are no data to suggest that 325 mg of aspirin is more efficacious than 81 mg at preventing restenosis in the first 24–48 hours.

With that in mind, when encountering a patient with a history of a reaction to aspirin, an attempt should be made to determine which category of reaction, as outlined previously, is likely to have occurred. Every attempt should be made to identify AERD and to obtain historical evidence as to whether a history of reactions or tolerance to any other NSAID exists.

LOCATION AND TIMING

The authors feel that for all patients with an unstable arterial lesion (evolving myocardial infarction, evolving transient ischemic attack or cerebrovascular accident, *etc.*), the intravascular intervention should occur first and considerations for challenge/desensitization should be secondary. This is predicated by the concern that in any patient, there is a real possibility of causing asthma or histamine-mediated coronary vasospasm, which in an already unstable patient could be catastrophic.

The location of the aspirin challenge/desensitization will vary depending on the nursing and monitoring resources available to the allergist. A one-to-one, constant nursing attendance is required, with the supervising physician immediately available. Modalities to treat potentially severe asthmatic and urticarial reactions must be available, including epinephrine. In our institution virtually all desensitization/oral challenge procedures occur in our outpatient clinic. However, it is recognized that in other clinics/practices this same approach to aspirin challenge/desensitization will be undertaken in a monitored hospital bed.

In a patient unstable enough that continued hospitalization is necessary for management of the underlying medical condition, the goal of successful aspirin administration is paramount and takes precedence over obtaining an accurate diagnostic aspirin challenge. For that reason, pretreatment with steroids, antihistamines, and montelukast should be considered in all such patients, with the caveat that in a heavily premedicated patient, the lack of any symptoms during the challenge/desensitization procedure can not be interpreted as a true "negative challenge" but could also represent a "silent desensitization/challenge." This has implications for future aspirin use if there is a lapse in aspirin administration.

We believe that the converse situation is true in patients that are stable for discharge from the hospital before aspirin challenge/desensitization. Nearly all of these patients referred to our clinic after hospitalizations are able to be desensitized in the outpatient setting. In this setting we believe that obtaining an accurate diagnosis is important and can safely be obtained by withholding steroid and antihistamine pretreatment and only using these as treatment modalities for patients who react.

ASPIRIN CHALLENGE/DESENSITIZATION PROTOCOL

Two very similar protocols can be considered depending on the suspicion of the type of previous reaction (Fig. 1):

1. Patients who are asthmatic should be screened for the likelihood of AERD. Many times, the patient history and reported recent tolerance of another NSAID can eliminate the possibility of AERD. With an equivocal history or uncertainty about the diagnosis, further evaluation for AERD should take place. This can be done by performing a nasal exam for polyps and obtaining Water's view sinus radiograph or computed tomography of the sinuses. If the sinuses are clear or a unilateral opacification is identified, the patient does not have AERD. With pansinusitis, even without prior exposure to aspirin, ~1/3 will have a respiratory reaction to aspirin, signaling the final quatrad of AERD (pansinusitis, nasal polyps, asthma, and aspirin-induced respiratory reaction).

For unstable patients who likely have AERD, the approach is as follows: pretreatment with oral montelukast at 10 mg, inhaled corticosteroid/long-acting β-agonist, systemic corticosteroids (usually i.v.), and antihistamines should be given to everyone. Then, using a pill cutter, give one-half of an 81-mg aspirin tablet. This is generally lower than the provoking dose of 60–90 mg that causes reactions in most AERD patients. This dose can then be repeated in 90 minutes. At this point the patient will have 81 mg of aspirin in their system and this 81-mg dose can be repeated daily. In the AERD patient, it is likely that they will react to the second dose of 40.5 mg of aspirin. Symptoms will generally be mild to moder-

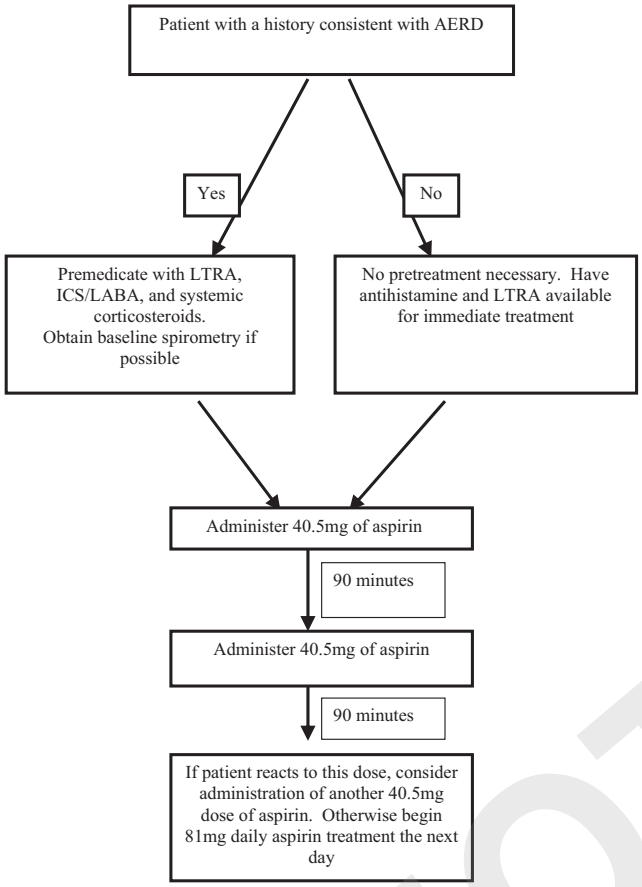


Figure 1. *Oral aspirin challenge/desensitization algorithm and protocol.*

ate but should be anticipated and promptly treated with nebulized β-agonists, oral or i.v. antihistamines, or other medications. A thorough review of the treatment or AERD reactions has been published.[16] If a reaction occurs after the first or second dose of aspirin, further dosing the following day should lead to minimal or no further symptoms. At a dose of 81 mg/day, some patients may not be completely desensitized, and care should be taken with higher doses of aspirin or other full strength NSAIDS. In a stable outpatient AERD desensitization, systemic corticosteroids may not be necessary and antihistamine use as pretreatment may mask symptoms of a reaction and create confusion over whether the patient truly has AERD.

2. For historical reactions of urticaria or rashes, challenge or desensitization can be started at the same doses. Pretreatment with an antihistamine and/or leukotriene receptor antagonist is likely to confuse negative reactions versus positive reactions but these should be added as soon as a cutaneous reaction occurs. A 40.5-mg dose of aspirin is appropriate and as per the protocol mentioned previously can be repeated in 90 minutes to reach the 81-mg target dose. This recommended challenge/desensitization protocol is predicated on the following premise: conclusive evidence that aspirin can induce IgE-mediated anaphylaxis remains elusive and may not even exist. But, if the presenting patient gives a history of, or emergency room records document a particularly severe prior aspirin reaction, starting with 20.25 mg of aspirin or less can be considered. Starting with an 81-mg aspirin tablet, a pill cutter can be used to obtain the 20.25-mg dose.

Some allergists follow the approach of Wong and colleagues.[7] The methodological flaws of this type of study have been outlined previously. Although this protocol is safe, it also starts at doses that are unnecessarily low and will delay the time to a therapeutic antiplatelet effect. With oral desensitizations that involve the hospital pharmacy, there can be a considerable delay in obtaining the required dilutions. In our experience, the majority of patients with a prior cutaneous reaction to another NSAID or a rash occurring >10 years previously and associated with ingesting aspirin will not react to 81 mg of aspirin.

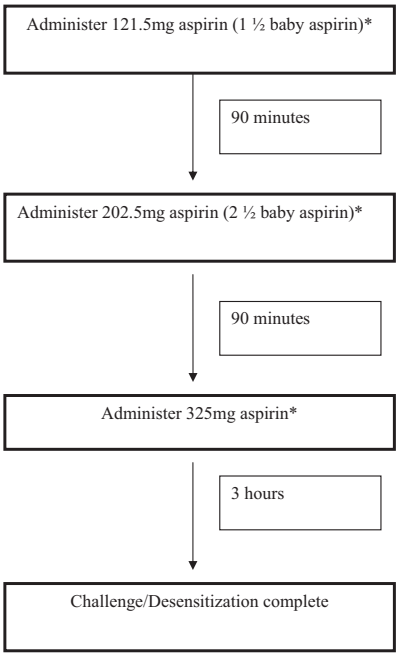
In summary, the approach to the patient with a previous aspirin reaction is to administer one-half a baby aspirin and repeat the dose in 90 minutes. It is only the difference in the character of the reaction that needs to be considered by the ordering physician.

PROCEEDING TO 325 MG OF ASPIRIN

Depending on the intervention, aspirin doses as high as 325 mg may be recommended by the referring cardiologist for optimum antiplatelet effect.[17] This dose can be achieved by continuing the aspirin dosing. Conversely, the patient may be discharged from the acute hospitalization on 81 mg of aspirin, and a follow-up visit may be made to increase the dose to 325 mg of aspirin. For all patients who have been taking 81 mg of aspirin uneventfully, they can undergo the rest of the challenge/desensitization in one outpatient clinic visit (Fig. 2).

PATIENTS THAT SHOULD NOT BE DESENSITIZED TO ASPIRIN

Nearly all patients with a history of a reaction to aspirin will be able to be properly evaluated with an oral challenge or desensitization. In a few circumstances the challenge/desensitization or challenge is "contraindicated." If there is a history of Steven's Johnson, toxic epidermal necrolysis, or DRESS syndrome, rechallenge can be dangerous and desensitization would be unsuccessful. Aspirin is a very unlikely candidate for the aforementioned reactions under any circumstances. Assuming linkage with aspirin, allergic interstitial nephritis and serum sickness will not be amenable to desensitization. Chronic urticaria represents a unique situation. Although desensitization can be safely attempted, in our experience, persistent recal-



*Symptoms should be treated if they occur. If severe symptoms occur at any dose, that dose should be repeated before proceeding to the final dose.

Figure 2. *Protocol to increase aspirin dose above 81mg (if desired).*

citrant urticaria and angioedema make long-term use of aspirin or NSAIDs very difficult if not impossible to manage. There is a report of one successful desensitization protocol[18] for a chronic urticaria patient requiring aspirin, but this case study can not be extrapolated to all patients with chronic hives.

In summary, with rare exceptions, patients with a history of "aspirin/NSAID allergy" will be able to safely take aspirin either after graded dose challenge or desensitization. Such an inexpensive and effective medication should not be withheld from most patients. A variety of protocols have been described, and although the exact mechanism of desensitization and patient characterization remains somewhat obscure, the take-home message is that in nearly all patients, negative challenge or desensitization was successful. Allergists should be proactive and consistent in their message that aspirin challenge/desensitization can be performed in the acute setting when clinically essential.

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